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METHOD AND SYSTEM FOR USE IN TREATING A PATIENT WITH AN ANTICOAGULANT TO OPTIMIZE THERAPY AND PREVENT AN ADVERSE DRUG RESPONSE

RELATED APPLICATION

The present patent application is a continuation-in-part of United States Patent Application Serial Number 09/348,592 filed on July 6, 1999, the entire contents of which are incorporated herein by reference thereto.

FIELD OF THE INVENTION

The present invention relates generally to a method and system for use in treating a patient with an anticoagulant to optimize drug therapy and to prevent an adverse drug response. More particularly, the present invention relates to a method and system for use in treating a patient with Coumadin® or a substance containing warfarin. The present invention can utilize either drug levels or other surrogate markers to determine the effectiveness of the dosing regimen and, if necessary, to suggest a new more optimal drug dose.

The term "anticoagulant" as used herein includes, but is not limited to, warfarin, Coumadin®, heparin, warfarin sodium salt, coumarin derivatives, indandione derivatives, dicumarol, anisindione, phenindione, ethyl bicoumacetate, bishydroxycoumarin, abcimixab, Reopro®, actilyse, alteplase, Activase®, anagrelide, Agrylin®, anistreplase, Eminase®, antithrombin III, Thrombate III®, ardeparin, Normiflo®, argatroban, clopidrogel, Plavix®, dalteparin, Fragmin®,

danaparoid, Orgaran®, dipyridamole, Persantine®, dipyridamole/aspirin, Aggrenox®, duteplase, enoxaparin, Lovenox®, eptifibatide, Integrilin®, lepirudin, Refludan®, nadroparin, Fraxiparine®, oprelvekin, Neumega®, pentosan polysulfate sodium, Elmiron®, reteplase, Retavase®, reviparin, Clivarine®, saruplase, streptokinase, Kabikinase®, Streptase®, tinzaparin, Innohep®, tirofiban, Aggrastat®, unfractionated heparin, low molecular weight heparin, all antithrombotic agents, all vitamin K antagonists, and all substances derived from and/or related to the foregoing substances.

Furthermore, wherever the generic term "anticoagulant" is used herein it is also intended to mean species which employ any or more of the individual anticoagulants as defined and/or alluded to hereinabove.

BACKGROUND OF THE INVENTION

When a patient begins taking an anticoagulant or any medication for a length of time, a titration of the amount of drug taken by the patient is necessary in order to achieve the optimal benefit of the drug, and at the same time to prevent any undesirable side effects that taking too much of the drug could produce. Thus, there is a continuous balance between taking enough drug in order to gain the benefits from that drug and at the same time not taking so much drug as to illicit a toxic event.

There is large inter-individual variability in the patient pharmocodynamic and pharmacokinetic interactions of drugs. What may be an appropriate drug dose for one individual, may be too much or too little for another. Prior to this invention a physician was required to estimate the correct drug dosage for a patient and then to experiment with that dosage, usually by trial and error, until the correct dosage was achieved. Likewise, the FDA labeling of a drug suggests dosages based on epidemiological studies and again does not account for inter-individual variability.

Non-linear least squares modeling methods involve the use of large amounts of data relating to a general population in order to calculate a best fit. Much like linear regression models, this method cannot take into account the variability between people with the same population characteristics.

Bayesian analysis is another method used to relate drug dose to efficacy. This method employs large-scale population parameters to stratify a population in order to better characterize the individuals. This method does not take into account the changes that can occur within a person over time, and as a result cannot reliably estimate dosages.

Pharmacokinetic compartment modeling has had success with some drugs, but because the models are static and cannot adapt themselves to changes within a population or a patient, they are once again undesirable for dynamically determining drug dosages.

Expert systems have been developed using similar technology to predict drug dosages for immunosuppressant drugs (see, e.g., U.S. Patent Nos. 5,365,948, 5,542,436 and 5,694,950). These algorithms, however, are not generic and only use immunosuppressant blood levels. Each algorithm is specific to an individual immunosuppressant drug. As it stands, these inventions cannot be applied to other drugs and do not have a non-linear feedback loop mechanism.

SUMMARY OF THE INVENTION

According to the present invention, patient dosing occurs through a cyclic series of events, depicted in flow chart form in Figure 1. After an initial examination, an initial dose of a drug, such as an anticoagulant, is prescribed and administered by a physician for a patient. The initial dose is based on the FDA recommended dosage found on the drug label. The anticoagulant dose is further refined upon repeated dosing by the physician based on the patient's response to the

anticoagulant. Too much anticoagulant could cause the patient to experience toxic anticoagulant effects, and the anticoagulant dose would need to be reduced. Too little anticoagulant could cause the patient not to receive the benefit the anticoagulant therapy could offer, and the dosage would need to be increased.

The preferred embodiment of the invention requires that a physician determine the percentage of response by the patient to the anticoagulant based on the surrogate markers for that anticoagulant. A relationship is then employed which uses the input parameters described above to determine the next dose for the patient.

The invention also includes embodiments focused on specific anticoagulants, such as, for example only, Coumadin®, warfarin, substances containing warfarin, etc. For example, the invention includes a method for calculating a revised dose of Coumadin® for a patient using Coumadin®, comprising the steps of: accepting as a first input the patient's current Coumadin® dose; accepting as a second input a maximum dose of Coumadin®; accepting as a third input a percent response of the patient based on one or more surrogate markers for said patient; and determining a revised dose, wherein said revised dose is a function of said current dose minus a ratio of the percent response of the patient and a ratio of said current dose to said maximum dose plus the percent of individual patient response multiplied by a response factor.

Another example is a method for determining a dose of warfarin or a substance containing warfarin for a patient, comprising the steps of: administering an initial dose of Warfarin or said substance containing warfarin to the patient; examining the patient to monitor and characterize one or more numerical surrogate markers; determining if a dose change is necessary; and calculating a revised dose as a function of said current dose minus the ratio of the change in numerical

markers and the ratio of said current dose to said maximum dose plus the percent of individual patient response multiplied by a response factor.

Each specie of the invention has two preferred embodiments; one which uses actual numerical surrogate markers to calculate a dose, and another embodiment that uses percentages as the numerical input for the surrogate markers.

DESCRIPTION OF THE DRAWINGS

Figure 1 shows a flow chart of the process by which revised doses of an anticoagulant are determined, according to the method of the invention described herein.

Figure 2 shows an apparatus for use in calculating revised doses of an anticoagulant according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

A method of this invention for use in treating a patient receiving an anticoagulant to optimize therapy and to prevent an adverse anticoagulant response can be implemented in two different embodiments, two of which will each be described separately. Figure 1 shows a flow chart of the overall process of treating a patient using this expert system. The actual expert system, however, performs only the steps shown in blocks 10 and 12 of the flow chart.

This expert system includes a general purpose computer, shown in Figure 2, comprising an input means, preferably a keyboard 20 and/or a mouse 22, an output means 30, preferably a video display screen, a data storage means 50, preferably a hard disk drive, and a processor. The expert computer program receives input data from a physician regarding the patient's current anticoagulant dose, the maximal dose range for the anticoagulant, and the percent response of the patient based on the surrogate markers used to monitor the anticoagulant. Also

characterized is the patient's response to the last dosing cycle as well as a dose response constant. This allows the expert system to individualize the patient dosing based on the patient's individual response to the anticoagulant. The system calculates a revised dosage based on the data input by the physician. The software portion of the invention includes a user interface portion 100 to receive the input data and to output the revised dosage information, and a data analysis portion 110, which calculates the new dosage information based on the input data.

Numerical Surrogate Markers Embodiment

A physician prescribes an anticoagulant for a patient based on the FDA recommended dose on the label of the anticoagulant. The physician then re-evaluates the patient, usually daily, either in person or remotely depending on the agent being prescribed. During the subsequent evaluations by the physician, the surrogate markers are monitored and sequentially compared to determine if there are any toxicities associated with the anticoagulant. Also the numerical markers will evaluated to see if the desired effect of the anticoagulant is being achieved. Based on this evaluation by the physician, the current anticoagulant dose, the current anticoagulant numerical marker, the desired anticoagulant numerical marker, and the previous anticoagulant numerical marker are then input into the embodiment and the new anticoagulant dose is calculated based on the equation:

$$NAD = CAD - \{[\langle(CANM - DANM)/CANM\rangle/\langle 1+ (CAD/HIGH)\rangle] \times CAD\} + LV$$

where:

$$LV = \{(RESPONSE \times CAD) \times [(1+D) - (1+E)]/ abs\ (1+D)\} / 1.3^{(CAD/HIGH)}$$

$$E = CANM - PANM$$

$$D = DANM - PANM$$

and wherein:

NAD = New Anticoagulant Dose

CAD = Current Anticoagulant Dose

CANM = Current Anticoagulant Numerical Marker

DANM = Desired Anticoagulant Numerical Marker

PANM = Previous Anticoagulant Numerical Marker

HIGH = The input parameter that is the high dose range for said anticoagulant

RESPONSE = Percent of total dose available for individualizing patient dose

abs = The absolute value of

1.3^(CAD/HIGH) = 1.3 raised to an exponent of (CAD/HIGH).

Percentage Surrogate Markers Embodiment

In this preferred embodiment, a physician prescribes an anticoagulant for a patient based on the FDA recommended dose on the label of the anticoagulant. The physician then re-evaluates the patient, usually daily, either in person or remotely depending on the agent being prescribed. During the subsequent evaluations by the physician, the surrogate markers are monitored and sequentially compared to determine if there are any toxicities associated with the anticoagulant. Also the surrogate markers are evaluated to see if the desired effect of the anticoagulant is being achieved. Based on this evaluation by the physician, the current anticoagulant dose, and the percent response of the patient to the last dosing based on a surrogate marker are then input into the system and the new anticoagulant dose is calculated based on the equation:

$$NAD = CAD - \{[\langle(PAR - 100)/PAR\rangle/\langle 1+ (CAD/HIGH)\rangle] \times CAD\} + LV$$

where:

$$LV = \{(RESPONSE \times CAD) \times [(100 - RES) \times 0.01]\} / 1.3^{(CAD/HIGH)}$$

and wherein:

NAD = New Anticoagulant Dose

CAD = Current Anticoagulant Dose

PAR = Percent response of patient to surrogate marker

RES = Percent response of patient to last dosing based on surrogate marker

HIGH = The input parameter that is the high dose range for said anticoagulant

RESPONSE = Percent of total dose available for individualizing patient dose

1.3^(CAD/HIGH) = 1.3 raised to an exponent of (CAD/HIGH).

This cycle of repeated re-evaluation of the numerical surrogate markers is continued as long as the patient is required to take the anticoagulant.

Two embodiments of the invention have been described, one using numerical markers, and one using a percentage surrogate marker.

Although the invention has been described in detail in the foregoing for the purpose of illustration, it is to be understood that such detail is solely for that purpose and that variations can be made therein by those of ordinary skill in the art without departing from the spirit and scope of the invention as defined by the following claims, including all equivalents thereof.